BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid which encodes a mammalian p-Hyde protein which induces susceptibility of a cancer cell to cell death, including analogs, fragments, variants, and mutants, thereof.

2. The isolated nucleic acid of claim 1, wherein the nucleic acid has a nucleic acid sequence having at least 75% similarity with the nucleic acid coding sequence of SEQ ID NOs: 1 or 5.

3. The isolated nucleic acid of claim 1, wherein the nucleic acid has a nucleic acid sequence having at least 85% similarity with the nucleic acid coding sequence of SEQ ID NOs: 1 or 5.

4. The isolated nucleic acid of claim 1, wherein the nucleic acid has a nucleic acid having at least 95% similarity with the nucleic acid coding sequence of SEQ ID NO:s 1 or 5.

5. The isolated nucleic acid of claim 1, wherein the nucleic acid fragment is set forth in SEQ ID NOs: 3 or 7.

6. The isolated nucleic acid of claim 1, wherein the nucleic acid fragment is set forth in SEQ ID NOs: 4 or 8.

7. The isolated nucleic acid of claim 1, wherein the nucleic acid is DNA or RNA

8. The isolated nucleic acid of claim 2, wherein the nucleic acid is cDNA or genomic DNA.

9. The isolated nucleic acid of claim 1, wherein the nucleic acid encodes an amino acid sequence having the sequence as set forth in SEQ ID NOs: 2 or 6.

10. The isolated nucleic acid of claim 1, wherein the nucleic acid is labeled with a detectable marker.

11. The isolated nucleic acid of claim 10, wherein the detectable marker is a radioactive, colorimetric, luminescent, fluorescent marker, or gold label.

12. An oligonucleotide of at least 15 nucleotides capable of specifically hybridizing with a sequence of the nucleic acid which encodes the human p-Hyde of claim 1.

13. The oligonucleotide of claim 12, wherein the nucleic acid is DNA or RNA.

14. The oligonucleotide of claim 12, wherein the oligonucleotide is labeled with a detectable marker.

15. The oligonucleotide of claim 13, wherein the oligonucleotide is a radioactive, colorimetric, luminescent, fluorescent marker, or gold label

16. A nucleic acid having a sequence complementary to the sequence of the isolated nucleic acid of claim 1.

17. An antisense molecule capable of specifically hybridizing with the isolated nucleic acid of claim 1.

18. A vector comprising the isolated nucleic acid of claim 1.

19. The vector of claim 18, further comprising a promoter of RNA transcription operatively, or an expression element linked to the nucleic acid.

20. The vector of claim 18, wherein the promoter comprises a bacterial, yeast, insect or mammalian promoter.

21. The vector of claim 20, wherein the vector is a plasmid, cosmid, yeast artificial chromosome (YAC), BAC, adenovirus, adeno-associated virus, retovirus, P1, bacteriophage or eukaryotic viral DNA.

22. The adenovirus vector of claim 21, wherein the adenovirus vector is a replication-deficient adenovirus type 5 expression vector.

23. The adenovirus vector of claim 22, wherein the adenovirus vector comprises an adenovirus genome having a deletion in the E1 and E3 region of the genome and an insertion within the region of a nucleic acid encoding p-Hyde, allele, fragment or variant thereof under the control of a promoter.

24. The vector of claim 23, wherein the promoter is a Rous Sarcoma virus promoter.

25. A host vector system for the production of a polypeptide which comprises the vector of claim 18 in a suitable host.

26. The host vector system of claim 25, wherein the suitable host is a prokaryotic or eukaryotic cell.

27. The host vector system of claim 26, wherein the eukaryotic cell is a yeast, insect, plant or mammalian cell.

28. A method for producing a polypeptide which comprises growing the host vector system of claim 18 under suitable conditions permitting production of the polypeptide and recovering the polypeptide so produced.

29. A method of obtaining a polypeptide in purified form which comprises:

(a) introducing the vector of claim 18 into a suitable host cell;

(b) culturing the resulting cell so as to produce the polypeptide;

(c) recovering the polypeptide produced in step (b); and

(d) purifying the polypeptide so recovered.

30. A polypeptide comprising the amino acid sequence of a mammalian p-Hyde.

31. The polypeptide of claim 30, wherein the amino acid sequence is set forth in SEQ ID NOs: 2 or 6.

32. A fusion protein or chimeric comprising the polypeptide of claim 30.

33. An antibody which specifically binds to the polypeptide of claim 30.

34. The antibody of claim 33, wherein the antibody is a monoclonal or polyclonal antibody.

35. A pharmaceutical composition comprising an amount of the polypeptide of claim 30 and a pharmaceutically effective carrier or diluent.

36. A transgenic, nonhuman mammal comprising the isolated nucleic acid of claim 1.

37. A method for determining whether a subject carries a mutation in the p-Hyde gene which comprises:

(a) obtaining an appropriate nucleic acid sample from the subject; and

(b) determining whether the nucleic acid sample from step (a) is, or is derived from, a nucleic acid which encodes mutant p-Hyde so as to thereby determine whether a subject carries a mutation in the p-Hyde gene.

38. The method of claim 37, wherein the nucleic acid sample in step (a) comprises mRNA corresponding to the transcript of DNA encoding a mutant p-Hyde, and wherein the determining of step (b) comprises:

(i) contacting the mRNA with the oligonucleotide of claim 12 under conditions permitting binding of the mRNA to the oligonucleotide so as to form a complex;

(ii) isolating the complex so formed; and

(iii) identifying the mRNA in the isolated complex so as to thereby determine whether the mRNA is, or is derived from, a nucleic acid which encodes mutant p-Hyde.

39. The method of claim 38, wherein the determining of step (b) comprises:

(i) contacting the nucleic acid sample of step (a), and the isolated nucleic acid of claim 1 with restriction enzymes under conditions permitting the digestion of the nucleic acid sample, and the isolated nucleic acid into distinct, distinguishable pieces of nucleic acid;

(ii) isolating the pieces of nucleic acid; and

(iii) comparing the pieces of nucleic acid derived from the nucleic acid sample with the pieces of nucleic acid derived from the isolated nucleic acid so as to thereby determine whether the nucleic acid sample is, or is derived from, a nucleic acid which encodes mutant p-Hyde.

40. A method for screening a tumor sample from a human subject for a somatic alteration in a p-Hyde gene in said tumor which comprises gene comparing a first sequence selected form the group consisting of a p-Hyde gene from said tumor sample, p-Hyde RNA from said tumor sample and p-Hyde cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of p-Hyde gene from a nontumor sample of said subject, p-Hyde RNA from said nontumor sample and p-Hyde cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the p-Hyde gene, p-Hyde RNA or p-Hyde cDNA from said tumor sample from the sequence of the p-Hyde gene, p-Hyde RNA or p-Hyde cDNA from said nontumor sample indicates a somatic alteration in the p-Hyde gene in said tumor sample.

41. A method for screening a tumor sample from a human subject for the presence of a somatic alteration in a p-Hyde gene in said tumor which comprises comparing p-Hyde polypeptide from said tumor sample from said subject to p-Hyde polypeptide from a nontumor sample from said subject to analyze for a difference between the polypeptides, wherein said comparing is performed by (i) detecting either a full length polypeptide or a truncated polypeptide in each sample or (ii) contacting an antibody which specifically binds to either an epitope of an altered p-Hyde polypeptide or an epitope of a wild-type p-Hyde polypeptide to the p-Hyde polypeptide from each sample and detecting antibody binding, wherein a difference between the p-Hyde polypeptide from said tumor sample from the p-Hyde polypeptide from said nontumor sample indicates the presence of a somatic alteration in the p-Hyde gene in said tumor sample.

42. A method for identifying a chemical compound which is capable inducing susceptibility to cell death which comprises:

(a) contacting the p-Hyde with a chemical compound under conditions permitting binding between the p-Hyde and the chemical compound;

(b) detecting specific binding of the chemical compound to the p-Hyde; and

(c) determining whether the chemical compound inhibits the p-Hyde so as to identify a chemical compound which is capable of capable inducing susceptibility to cell death.

43. A method of inhibiting the growth of cancer cells, comprising the steps of obtaining the cells and contacting the cells of the subject with a replication-deficient adenovirus type 5 expression vector comprising an adenovirus genome having a deletion in the E1 and E3 region of the genome and an insertion within the region of a nucleic acid encoding p-Hyde under the control of a Rous Sarcoma virus promoter, thereby inhibiting the growth of the cancer cells.

44. A method of inhibiting the growth a cancer cells, comprising: 1) obtaining a sample of prostate cells from a subject; 2) contacting the cells with a replication deficient adenovirus type 5 expression vector which comprises an adenovirus genome having a deletion in the E1 and E3 regions of the genome and an insertion within the regions of a p-Hyde cDNA under the control of a Rous Sarcoma virus promoter; and 3) introducing the cells into the subject, thereby inhibiting the growth of the cancer cells.

45. A method of suppressing the growth of cancer cells in a subject, comprising introducing into the cancer cell an amount of a nucleic acid encoding a p-Hyde protein, a nucleic acid encoding a fragment of p-Hyde protein, or the nucleic acid encoding a mutant p-Hyde protein, thereby suppressing the growth of cancer cells in the subject.

46. A method of suppressing growth of cancer cells in a subject, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a nucleic acid encoding a p-Hyde protein, a nucleic acid encoding a fragment of p-Hyde protein, or the nucleic acid encoding a mutant p-Hyde protein and a pharmaceutical acceptable carrier or diluent, thereby suppressing the growth of cancer cells in the subject.

47. A method of inducing susceptibility to apoptosis of cancer cells in a subject, comprising introducing into the cancer cell an amount of a nucleic acid encoding a p-Hyde protein, a nucleic acid encoding a fragment of p-Hyde protein, or the nucleic acid encoding a mutant p-Hyde protein, thereby inducing susceptibility to apoptosis.

48. A method of inducing susceptibility to apoptosis of cancer cells in a subject, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a nucleic acid encoding a p-Hyde protein, a nucleic acid encoding a fragment of p-Hyde protein, or the

nucleic acid encoding a mutant p-Hyde protein and a pharmaceutical acceptable carrier or diluent, thereby inducing susceptibility to apoptosis.

49. A method of treating a subject with cancer which comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a nucleic acid encoding a p-Hyde protein, a nucleic acid encoding a fragment of p-Hyde protein, or the nucleic acid encoding a mutant p-Hyde protein and a pharmaceutical acceptable carrier or diluent, thereby treating the subject with cancer.

50. A method of treating a subject with cancer, comprising: 1) administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a nucleic acid encoding a p-Hyde protein, a nucleic acid encoding a fragment of p-Hyde protein, or the nucleic acid encoding a mutant p-Hyde protein in combination with radiation, chemotherapy, or UV mimetic drugs; and 2) a pharmaceutical acceptable carrier or diluent, thereby treating the subject with cancer.

51. A method of treating a subject with cancer, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising: 1) an adenovirus type 5 expression vector which comprises an adenovirus genome having a deletion in the E1 and E3 regions of the genome and an insertion within the regions of a full length sense p-Hyde cDNA under the control of a Rous Sarcoma virus promoter, and 2) a suitable carrier or diluent, thereby treating the subject with cancer.

52. The method of claims 43- 51, wherein the cancer is selected from a group consisting of: melanoma; lymphoma; leukemia; and prostate, colorectal, pancreatic, breast, brain, or gastric carcinoma.

53. The method of claim 50, wherein the pharmaceutical composition is administered parenterally, paracancerally, transmucosally, transdermally, intramuscularly, intravenously, intradermaly, subcutaneously, intraperitonealy, intraventricularly, or intracranialy.

add
C²